

44 100. (Amended) A method according to claim 96, wherein administration is by means of a pharmaceutical composition in unit dosage form [which contains] comprising the said [quinuclidine derivative] compound in an amount [in the range of] ranging from about 0.5 to about 500 mg., together with an inert carrier or diluent. *62*

Please add the following new claim:

15 *47* --101. The compound 3-hydroxy-3-mercaptomethyl quinuclidine.--.

REMARKS

The Amended Application

The amendments to the specification and claims are responsive to all of the Examiner's objections under 35 U.S.C. §112. The specification, as amended, describes the invention in such full, clear, concise, and exact terms as to enable those skilled in the art to make and use the invention, and the claims particularly point out and distinctly claim the subject matter which applicants regard as the invention.

On page 6 of the specification, formula (I) is amended to change the Z group to a carbon atom substituted by an R¹ group and an R² group. Accordingly, the definition of the Z group is

removed at page 6 and elsewhere in the specification. The claims have been amended in the same manner.

Claim 1 has been amended to change "quinuclidine derivatives having the general formula (I)" to "a compound of the formula (I)". The remaining claims are amended consistent with claim 1. Instead of claiming the compound 3-hydroxy-3-mercaptomethyl quinuclidine by defining Z as two hydrogen atoms, the compound is recited as new independent claim 101. Contrary to the Examiner's statement (page 2, lines 19-21 of the Official Action), the compound of formula (I) in which R¹ and R² are both hydrogen is not encompassed within the present invention.

In claim 1 and the remaining claims, the term "alkyl" is amended to read "lower alkyl". This amendment is supported by the disclosure at page 7, where the righthand column of the table shows that R¹ and R² may be methyl, ethyl or propyl. It is submitted that the meaning of the term "lower alkyl" is known to those skilled in the art and is found in thousands of issued patents, including Cohen et al. cited by the Examiner. The term "aryl" has been changed to "phenyl". This amendment is supported by the specification at page 7, where phenyl is shown in both columns of the table describing the R¹ and R² substituents. The term "diaryl methylol" is changed to "diphenylmethylol", which is also shown in the table on page 7 of the specification. The terms "alkyl which is substituted by one or more aryl groups" is changed to "lower alkyl which is substituted by one or two

groups"; these terms are supported by the disclosure of diphenylmethyl shown in the table on page 7 of the specification. Thus, the Examiner's objection to the term "or more" is avoided. The term "1-pyrenepropyl" has been deleted from claims 8 and 54.

The Examiner's objection to the term "pharmaceutical" as too vague or indefinite to constitute a utility is not understood. The utility of the claimed compound and composition need not be recited in the claims. The description of utility set forth in the specification satisfies the minimal utility requirement of 35 U.S.C. §101. The method of use claims describe the manner in which the claimed compounds and compositions are to be used with sufficient particularity and distinctness to satisfy the requirements of 35 U.S.C. §112.

Claims 57-59 specifically recite "a method for treating diseases of the central nervous system in mammals" and are supported by the specification at pages 20 and 62-79. Claims 60-61 and 68 specifically recite "a method for treating diseases due to a deficiency in the central cholinergic system in mammals" and are supported by the specification at page 20. Claims 60-62 and 68 specifically recite "a method for treating diseases due to a deficiency in the central cholinergic system in mammals" and are supported by the specification at page 20. Claims 63-67 and 69-71 specifically recite "a method for treating diseases due to cholinergic hyperfunction in mammals" and are supported by the

specification at page 21. Claims 72-74 specifically recite "a method for treating senile dementia of Alzheimer's type" and are supported by the specification at page 21. Thus, the method of use of the compounds of the present invention are particularly pointed out and distinctly claimed as well as fully supported by the specification.

There are no prior art rejections of claims 1-17, 42-54, 57-86 and 88-100. Therefore the foregoing amendments place these claims in condition for allowance.

Traversing the Prior Art Rejection

The Examiner has rejected claims 18-42, directed to the process for synthesizing the novel compounds of the present invention, under 35 U.S.C. §103 as unpatentable over Cohen et al. U.S. Patent 4,104,397. The Examiner alleges that "the process of reacting an aldehyde or ketone with 3-hydroxymethyl-3-hydroxyquinuclidine to form a 2-methylspiro(1,3 dioxolane-4,3')quinuclidine", shown in Cohen et al., "is entirely analogous with the process claimed." This rejection is respectfully traversed on the following grounds.

In Example 1 of Cohen et al., 3-carbomethoxy-3-quinuclidinol is reduced to 3-hydroxymethyl-3-quinuclidinol, which is then reacted with acetaldehyde in the presence of BF₃ etherate to give 2-methylspiro(1,3-dioxolane-4,3')quinuclidine. In Example 2 of the cited patent, "quinuclidine-3-epoxide" is

prepared, which is then reacted with acetone in the presence of BF_3 -etherate to give 2,2,-dimethylspiro(1,3 -dioxolane-4,3') quinuclidine. In Example 3, benzophenone is reacted by the method of either Example 1 or 2 to give 2,2, -diphenylspiro(1,3-dioxolane-4,3')quinuclidine.

In the present application, a novel compound 3-hydroxy-3-mercaptopquinuclidine is first prepared by reacting the epoxide with HS. At this stage there is no analogy whatever to the cited patent. An analogous step would be to react the epoxide with water to obtain the analogous diol, but this is not taught in Cohen et al. Therefore, even if the argument in the Official Action on grounds of pure analogy is correct in principle, which is not conceded by Applicants, the obviousness rejection is improper at least with respect to claims 32 to 41, which depend on the epoxide/ H_2S reaction, because no analogous reaction is taught in the citation.

According to claims 18-31 in a second stage, of the present invention, the mercapto alcohol obtained in the first stage is reacted with an appropriate carbonyl compound. It is agreed that superficially this second stage is analogous to the process described in Example 1 of Cohen et al. However, it is submitted that this analogy does not render the invention of present claims 18-41 obvious. It is well established that "obvious to try" (to one skilled in the art) is not a proper criterion to prove obviousness. Rather, the standard of

obviousness is that the prior art should "suggest" the invention in question. In this connection, the cited patent nowhere suggests that the substitution of sulfur for oxygen would give analogous results in the processes described therein. Moreover, knowledge of the general prior art combined with the citation could not "suggest" the present process to one skilled in the art, insofar as the required starting material for the second stage of the present process, which the Examiner argues is analogous to the citation, did not exist in the realm of the prior art.

It is also noted that the product of the allegedly obvious process is in itself novel and inventive, as are additionally, the therapeutic method utilizing the product. It is believed that a process such as that presently under consideration, wherein at the material time neither the starting material (the hydroxymercaptoquinuclidine) nor the end product (the spiro oxathiolane) were within the realm of known art, and where the analogy on which it is depended to establish a finding of obviousness - the substitution of sulfur for oxygen - is not present in the cited document, cannot reasonably be regarded as being obvious within the meaning of 35 U.S.C. §103. For all the foregoing reasons, it is believed that the rejection of claims 18-41 should be withdrawn.

New drawings will be filed when the application is deemed otherwise in order for allowance.

Abraham FISHER, et al. - U.S. Serial No. 853,404

In view of the foregoing amendments and arguments, the claims are believed to be allowable and the application is considered to be in condition for allowance. Favorable reconsideration and allowance of the application is respectfully requested.

Respectfully submitted,

CUSHMAN, DARBY & CUSHMAN

By Carl G. Love #1881
Carl G. Love
Reg. No. 18,781

CGL/EAM:efc

1615 L Street, NW
Eleventh Floor
Washington, DC 20036-5601
(202) 861-3000